Quantitative Systems Pharmacology Modeling of CAR-T Therapy and T Cell Engaging Bispecific Antibodies: B-cell Acute Lymphoblastic Leukemia Case Study

InSysBio
QSP Company

Oleg Demin Jr, Antonina Nikitich

InSysBio, Moscow, Russia

INTRODUCTION

Currently there are a lot of therapies (bispecific mAbs, CAR-T, etc) for acute lymphoblastic leukemia (ALL) treatment targeting CD19, CD20 or CD22. The aim of this study is to understand what is the better target for treatment of ALL with bispecific antibodies and CAR-T using quantitative systems pharmacology (QSP) model of ALL and its treatment with blinatumomab (CD3/CD19 bispecific antibody) and CD19 CAR-T (19-28z CAR-T developed in Memorial Sloan Kettering Cancer Center).

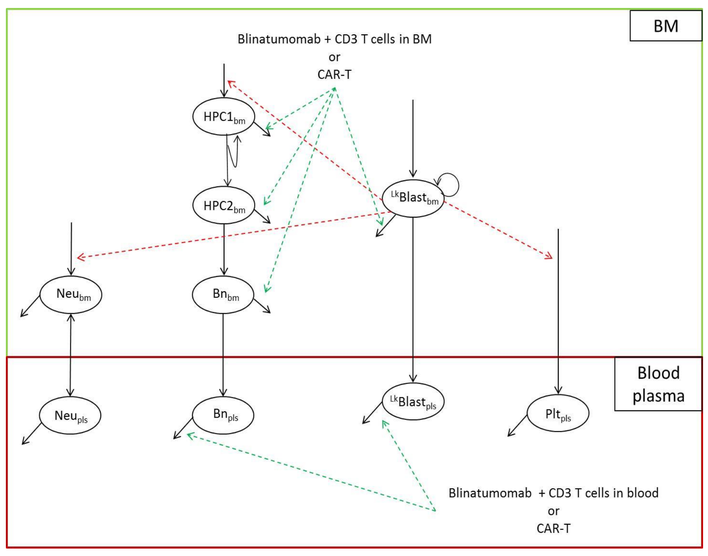
MODEL DESCRIPTION

Model was developed on the basis of Immune Response Template [IRT] (irt.insysbio.ru). Model describes hematopoiesis of normal B cells, leukemic blasts, neutrophils, platelets, CD4 and CD8 T cells, different cytokines (IL-2, IL-6, TGFb, TNFa, IFNg) in physiological compartments (bone marrow (BM), blood/plasma).

Blinatumomab stimulates specific lysis of CD19+ cells (leukemic blasts, normal B cell precursors and naïve B cells) by CD3+ cells (CD8 and CD4 T cells) and activation of CD8 and CD4 T cells (only in presence of CD19+ cells). Blinatumomab effect depends on concentration of trimer complex (CD19-blin-CD3) described in the model. Only activated T cells (not resting) are able to produce cytokines. Also, activated T cells could adhere to epithelial cells of blood vessels (marginated pool of cells). Model takes into account pre-treatment of patients with dexamethasone and cyclophosphamide.

Description of CAR-T cells is similar to non-modified T cells, except CAR-T cells could kill CD19+ cells without blinatumomab.

Normal hematopoiesis and leukemic blasts



HPC1 = **CD20 negative** precursors of B cells (CD19+/CD20-/CD22+)

HPC2 = **CD20 positive** precursors of B cells (CD19+/CD20+/CD22+)

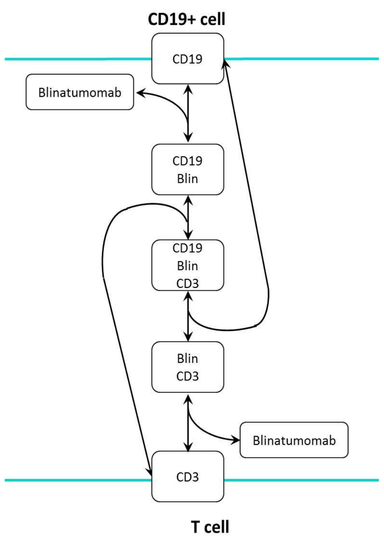
Bn – naïve B cells (CD19+/CD20+/CD22+)

Blast – leukemic blasts (CD19+CD20+/CD22+) – in this version of the model it is assumed that all leukemic blasts are CD19+/CD20+/CD22+

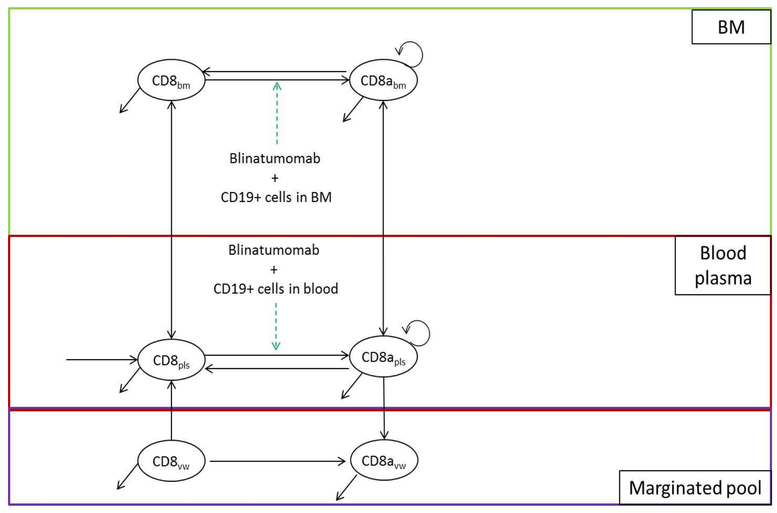
Neu – neutrophils

Plt - platelets

CD19 : blinatumomab : CD3 complex



CD8 T cells



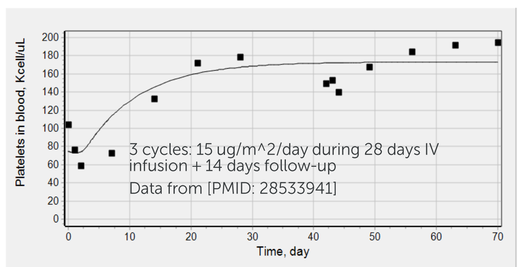
Scheme for CD4 T cells is the same as for CD8 T cells

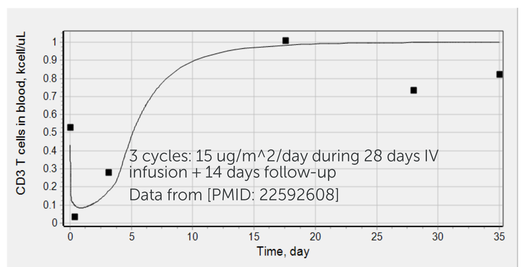
Parameters describing normal hematopoiesis, T cells and cytokines were calculated on the basis of the data on levels of cells and cytokines in blood/plasma and BM of healthy subjects. Parameters related to leukemic blasts were estimated against in vitro data and then re-calibrated against data on cells and cytokines levels in blood/plasma and BM of relapsed/refractory (r/r) ALL patients. Parameters describing ALL progression was estimated on the basis of the data on dynamics of blasts in BM during relapse in AML/T-ALL patients.

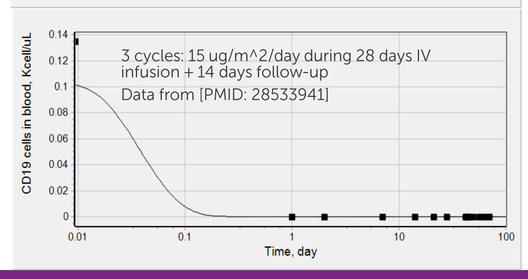
Generally, model describes 2 types of virtual patients (VP): **healthy subject** and **r/r B-cell ALL**.

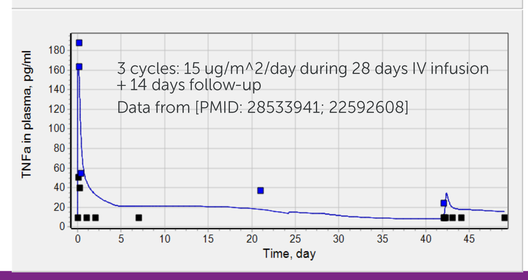
DESCRIPTION OF BLINATUMOMAB DATA

Blinatumomab parameters were partially fitted against in vitro data (T cells were cultured with CD19+ ALL cells lines or CD19+ cells in presence of blinatumomab). Some parameters were taken from IRT. Other part of parameters (including some parameters identified against in vitro data) were calibrated/validated against clinical data. Examples:









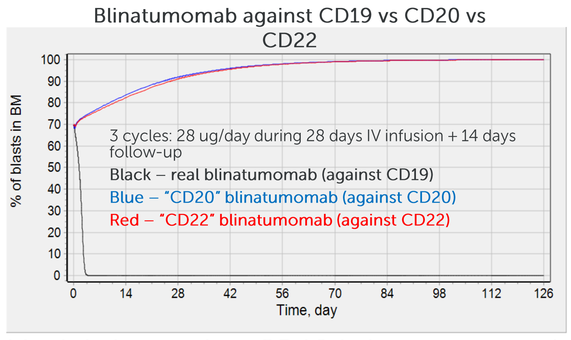
SIMULATIONS: PRIORITIZATION OF CD19, CD20, CD22

To evaluate CD19, CD20 and CD22 as a target for treatment of B-cell ALL we simulate treatment of r/r B-cell ALL VP with:

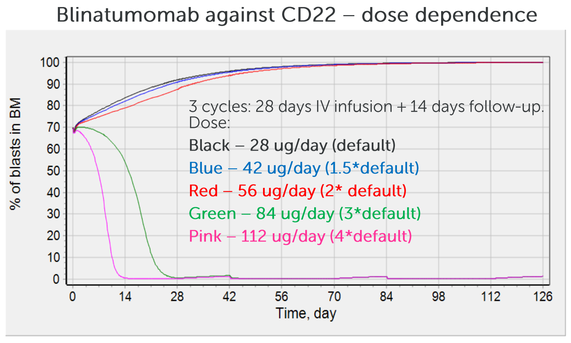
- blinatumomab (targeted CD19+ cells),
- "CD20" blinatumomab (similar to real blinatumomab, but targeting CD20+ cells),
- "CD22" blinatumomab (similar to real blinatumomab, but targeting CD22+ cells).

It is assumed that all **leukemic blasts are CD19+/CD20+/CD22+**. The number of CD19, CD20 and CD22 molecules on leukemic blasts and normal B cells were taken from the literature (data on number of CD20 molecules shows high variability).

Blinatumomab against CD19 vs CD20 vs CD22



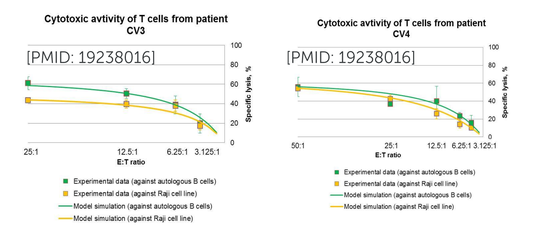
Blinatumomab against CD22 – dose dependence

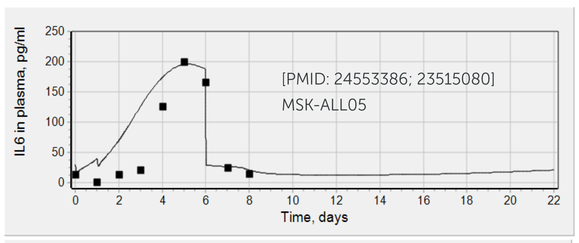


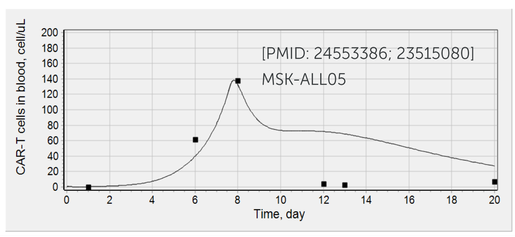
Model shows that CD19 is better target than CD20 and CD22 due to the its highest expression on leukemic blasts. But if the dose of bispecific antibody is significantly increased, level of leukemic blast goes to 0 even if blinatumomab targets CD20 or CD22.

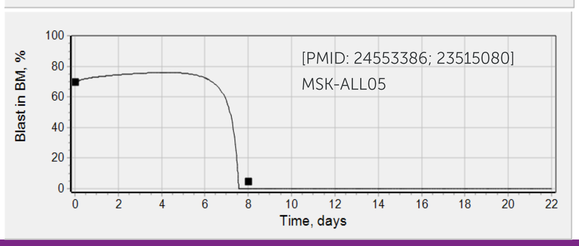
DESCRIPTION OF CD19 CAR-T DATA

CAR-T parameters were partially fitted against in vitro data (CAR-T cells were cultured with CD19+ ALL cells lines or CD19+ cells form CLL patients). Some parameters were taken from IRT. Then, other part of parameters (including some parameters identified against in vitro data) were calibrated/validated against CAR-T clinical data. Examples:









CONCLUSIONS

CD19 is better target for B-cell ALL treatment in general population of patients. The number of CD19, CD20, CD22 molecules on leukemic blast of particular patient could be used as a predictive marker and a way how to choose the target for therapy.

CONTACTS

For more information, please visit our web site at **www.insysbio.com**.
Oleg Demin Jr by e-mail: **demin_jr@insysbio.com.**